

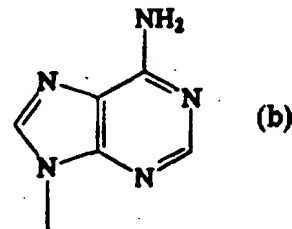
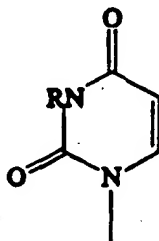
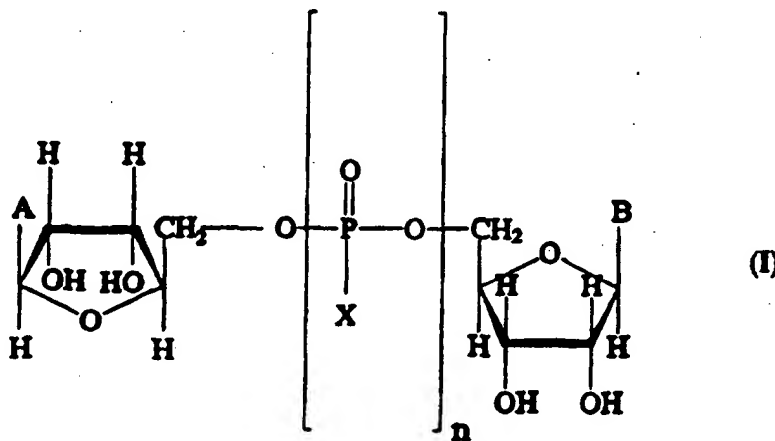
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Published With international search report.			

(54) Title: DINUCLEOTIDES USEFUL FOR THE TREATMENT OF LUNG DISEASE

(57) Abstract

A compound of Formula (I), or a pharmaceutically acceptable salt thereof, is disclosed. In a compound of Formula (I): n is from 1 to 6; n is preferably from 2 to 4, and is most preferably 4. X is -OH or -SH, and is preferably -OH. A and B are each independently selected from the group consisting of (a) and (b) wherein R is H or Br. The compounds are useful in the treatment of airway diseases such as cystic fibrosis. Further disclosed are pharmaceutical formulations comprising, in pharmaceutically acceptable carriers (e.g., solid or liquid carriers), a compound of Formula (I) as given above. A method of hydrating mucous secretions in the lungs of a subject in need of such treatment, comprising administering to the lungs of the subject a compound of Formula (I) as given above, is also disclosed. The administering step is preferably carried out by inhalation.



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DINUCLEOTIDES USEFUL FOR THE TREATMENT OF LUNG DISEASE

Field of the Invention

This invention relates to certain dinucleotides, pharmaceutical formulations containing the same, and methods of removing retained mucus secretions from the lungs of a subject by administering
5 dinucleotides to the subject.

Background of the Invention

This invention was made with government support under Grant No. MHLBIHL34322 awarded by the National
10 Institutes of Health. The government has certain rights in the invention.

In cystic fibrosis several functions of airway epithelia are abnormal, and deficiencies in both Cl^- transport and Na^+ absorption are well documented. See,
15 e.g. Knowles et al., *Science* 221, 1067 (1983); Knowles et al., *J. Clin. Invest.* 71, 1410 (1983). Regulation of ion transport might have potential therapeutic benefit in lung diseases characterized by abnormalities in epithelial ion transport, e.g., cystic fibrosis.

20 One therapeutic goal in cystic fibrosis and other pulmonary diseases in which the water content of the mucous is altered is to hydrate the lung mucous secretions, so that the secretions may be thereafter more easily removed from the lungs by mucociliary action or
25 simple coughing. The use of aerosolized amiloride to hydrate mucous secretions is described in U.S. Patent No. 4,501,729. Amiloride appears to block Na^+ reabsorption

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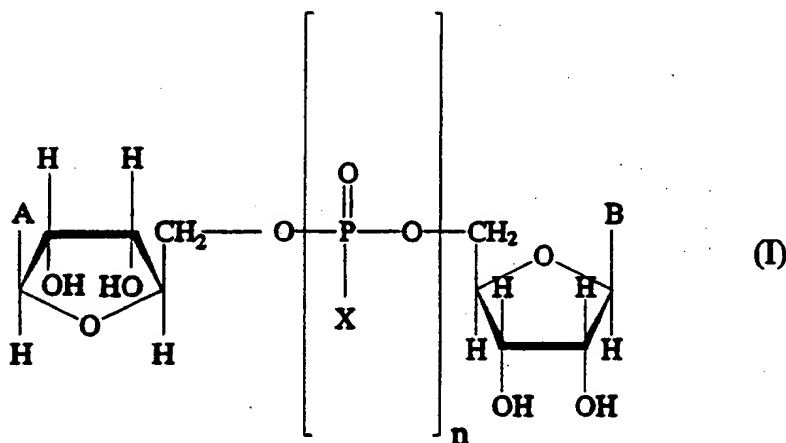
by airway epithelial cells, and therefore inhibits water absorption from the mucous.

A different therapeutic approach for hydrating lung mucous secretions is exemplified by techniques that involve the administration of ATP or UTP, which appear to stimulate chloride secretion from respiratory epithelial cells. See, e.g., U.S. Patent No. 5,292,498 to Boucher.

In view of the large numbers of people afflicted with cystic fibrosis, there is an ongoing need for new methods for providing methods of hydrating lung mucous secretions and thereby facilitating lung mucous clearance.

Summary of the Invention

A first aspect of the present invention is a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



In a compound of Formula I:

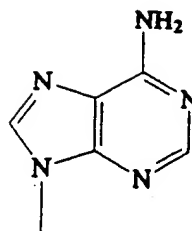
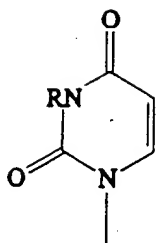
n is from 1 to 6. n is preferably from 2 to 4, and is most preferably 4.

X is -OH or -SH, and is preferably -OH.

A and B are each independently selected from the group consisting of:

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and



wherein R is H or Br.

A second aspect of the present invention is a pharmaceutical formulation comprising, in a pharmaceutically acceptable carrier (e.g., a solid or liquid carrier), a compound of Formula (I) as given above or a pharmaceutically acceptable salt thereof in an amount effective to hydrate lung mucous secretions. Optionally, the pharmaceutical formulation may further comprise a compound selected from the group consisting of amiloride, benzamil and phenamil in an amount effective to inhibit the reabsorption of water from lung mucous secretions.

A third aspect of the present invention is a method of hydrating mucous secretions in the lungs of a subject in need of such treatment, comprising administering to the lungs of the subject a compound of Formula I as given above, or a pharmaceutically acceptable salt thereof, in an amount effective to hydrate lung mucous secretions.

A fourth aspect of the present invention is the use of a compound of Formula I as given above, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for hydrating mucous secretions in the lungs of a subject in need of such treatment.

The foregoing and other objects and aspects of the present invention are explained in detail in the specification set forth below.

Brief Description of the Drawings

Figure 1 shows the effect of dinucleotide A_2P_4 on Cl^- secretion on the luminal surface of airway epithelia previously treated with forskolin.

5 Figure 2 shows the effect of A_2P_4 administration on Cl^- secretion in airway epithelia prestimulated with UTP.

Detailed Description of the Invention

The method of the present invention can be used
10 to facilitate (i.e., enhance, speed, assist) the clearance of mucous secretions from the lungs of a subject in need of such treatment for any reason, including (but not limited to) retained secretions arising from airway diseases such as cystic fibrosis,
15 chronic bronchitis, asthma, bronchiectasis, post-operative atelectasis (plugging of airways with retained secretions after surgery), and Kartagener's syndrome.

The present invention is concerned primarily with the treatment of human subjects, but may also be
20 employed for the treatment of other mammalian subjects, such as dogs and cats, for veterinary purposes.

Compounds of Formula I and the pharmaceutically acceptable salts thereof (i.e., active compounds) may be prepared in accordance with the techniques described
25 herein and variations thereof which will be apparent to those skilled in the art. As an example, synthesis of UpppppU (U_2P_4) may be carried out by condensation of UDP using the water soluble carboimide EDC (1-ethyl-3-[3-dimethyl-ammonio-propyl]-carboimide hydrochloride). See
30 K.E. Ng and L.E. Orgel, *Nucleic Acids Research* 15(8), 3572-80 (1987).

Amiloride and its use in hydrating lung mucus secretions is known and described in U.S. Patent No. 4,501,729 to Boucher and Knowles (all patent references
35 recited herein are to be incorporated by reference herein in their entirety). Benzamil (also known as 3,5-diamino-

6-chloro-N-(benzylaminoaminomethylene) pyrazinecarboxamide) and phenamil (also known as 3,5-diamino-6-chloro-N-(phenylaminoaminomethylene)pyrazinecarboxamide) are known compounds and are disclosed in U.S. Patent No. 3,313,813 to E. Cragoe. The terms "benzamil", "phenamil", and "amiloride", as used herein, include the pharmaceutically acceptable salts thereof (i.e., salts as given above), such as (but not limited to) amiloride hydrochloride, benzamil hydrochloride or phenamil hydrochloride.

Active compounds of the present invention may, as noted above, be prepared as pharmaceutically acceptable salts thereof. Pharmaceutically acceptable salts are salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects. Examples of such salts are (a) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; and salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; and (b) salts formed from elemental anions such as chlorine, bromine, and iodine.

The active compounds disclosed herein may be administered to the lungs of a subject by any suitable means, but are preferably administered by administering an aerosol suspension of respirable particles comprised of the active compound, which the subject inhales. The respirable particles may be liquid or solid.

Aerosols of liquid particles comprising the active compound may be produced by any suitable means,

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such as with a pressure-driven aerosol nebulizer or an ultrasonic nebulizer. See, e.g., U.S. Patent No. 4,501,729. Nebulizers are commercially available devices which transform solutions or suspensions of the active ingredient into a therapeutic aerosol mist either by means of acceleration of compressed gas, typically air or oxygen, through a narrow venturi orifice or by means of ultrasonic agitation. Suitable formulations for use in nebulizers consist of the active ingredient in a liquid carrier, the active ingredient comprising up to 40% w/w of the formulation, but preferably less than 20% w/w. The carrier is typically water (and most preferably sterile, pyrogen-free water) or a dilute aqueous alcoholic solution, preferably made isotonic with body fluids by the addition of, for example, sodium chloride. Optional additives include preservatives if the formulation is not made sterile, for example, methyl hydroxybenzoate, antioxidants, flavoring agents, volatile oils, buffering agents and surfactants.

Aerosols of solid particles comprising the active compound may likewise be produced with any solid particulate medicament aerosol generator. Aerosol generators for administering solid particulate medicaments to a subject produce particles which are respirable, as explained above, and generate a volume of aerosol containing a predetermined metered dose of a medicament at a rate suitable for human administration. One illustrative type of solid particulate aerosol generator is an insufflator. Suitable formulations for administration by insufflation include finely comminuted powders which may be delivered by means of an insufflator or taken into the nasal cavity in the manner of a snuff. In the insufflator, the powder (e.g., a metered dose thereof effective to carry out the treatments described herein) is contained in capsules or cartridges, typically made of gelatin or plastic, which are either pierced or opened *in situ* and the powder delivered by air drawn

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through the device upon inhalation or by means of a manually-operated pump. The powder employed in the insufflator consists either solely of the active ingredient or of a powder blend comprising the active ingredient, a suitable powder diluent, such as lactose, and an optional surfactant. The active ingredient typically comprises from 0.1 to 100 w/w of the formulation. A second type of illustrative aerosol generator comprises a metered dose inhaler. Metered dose inhalers are pressurized aerosol dispensers, typically containing a suspension or solution formulation of the active ingredient in a liquified propellant. During use these devices discharge the formulation through a valve adapted to deliver a metered volume, typically from 10 to 150 μ l, to produce a fine particle spray containing the active ingredient. Suitable propellants include certain chlorofluorocarbon compounds, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and mixtures thereof. The formulation may additionally contain one or more co-solvents, for example, ethanol, surfactants, such as oleic acid or sorbitan trioleate, antioxidants and suitable flavoring agents.

The aerosol, whether formed from solid or liquid particles, may be produced by the aerosol generator at a rate of from about 10 to 150 liters per minute, more preferably from about 30 to 150 liters per minute, and most preferably about 60 liters per minute. Aerosols containing greater amounts of medicament may be administered more rapidly.

The dosage of the compound of Formula I, or pharmaceutically acceptable salt thereof, will vary depending on the condition being treated and the state of the subject, but generally may be an amount sufficient to achieve dissolved concentrations of active compound on the airway surfaces of the subject of from about 10^{-7} to about 10^{-3} Moles/liter, and more preferably from about 10^{-6}

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to about 3×10^{-4} Moles/liter. Depending upon the solubility of the particular formulation of active compound administered, the daily dose may be divided among one or several unit dose administrations. The daily
5 dose by weight may range from about 1 to 20 milligrams of respirable particles for a human subject, depending upon the age and condition of the subject. Amiloride, benzamil or phenamil administered concurrently with the compound of Formula I or salt thereof may be given in the
10 same dosages as the compound of Formula I or salt thereof.

Solid or liquid particulate pharmaceutical formulations containing active agents of the present invention should include particles of respirable size:
15 that is, particles of a size sufficiently small to pass through the mouth and larynx upon inhalation and into the bronchi and alveoli of the lungs. In general, particles ranging from about 1 to 5 microns in size (more particularly, less than about 4.7 microns in size) are
20 respirable. Particles of non-respirable size which are included in the aerosol tend to be deposited in the throat and swallowed, and the quantity of non-respirable particles in the aerosol is preferably minimized. For nasal administration, a particle size in the range of 10-
25 $500\mu\text{m}$ is preferred to ensure retention in the nasal cavity.

In the manufacture of a formulation according to the invention, active agents or the physiologically acceptable salts or free bases thereof are typically
30 admixed with, inter alia, an acceptable carrier. The carrier must, of course, be acceptable in the sense of being compatible with any other ingredients in the formulation and must not be deleterious to the patient. The carrier may be a solid or a liquid, or both, and is
35 preferably formulated with the compound as a unit-dose formulation, for example, a capsule, which may contain from 0.5% to 99% by weight of the active compound. One

or more active compounds may be incorporated in the formulations of the invention, which formulations may be prepared by any of the well-known techniques of pharmacy consisting essentially of admixing the components.

5 Compositions containing respirable dry particles of active compound may be prepared by grinding the active compound with a mortar and pestle, and then passing the micronized composition through a 400 mesh screen to break up or separate out large agglomerates.

10 Amloride, benzamil or phenamil used to prepare compositions for the present invention may alternatively be in the form of a pharmaceutically acceptable free base of benzamil or phenamil. Because the free base of the compound is less soluble than the salt, free base
15 compositions are employed to provide more sustained release of benzamil or phenamil to the lungs. Amloride, benzamil or phenamil present in the lungs in particulate form which has not gone into solution is not available to induce a physiological response, but serves as a depot of
20 bioavailable drug which gradually goes into solution.

The pharmaceutical composition may optionally contain a dispersant which serves to facilitate the formation of an aerosol. A suitable dispersant is lactose, which may be blended with the benzamil or
25 phenamil in any suitable ratio (e.g., a 1 to 1 ratio by weight).

The present invention is explained in greater detail in the following non-limiting Example.

EXAMPLE 1

30 Effect of dinucleotide A_2P_4 on chloride (Cl^-) secretion

Normal airway cells were cultured on permeable supports and Cl^- secretion assayed as previously described in M.J. Stutts, et al., *Am. J. Physiol.* 267, C1442-C1451 (1994). Cl^- secretion was measured after administration
35 of the dinucleotide A_2P_4 (Sigma Chemicals, St. Louis, MO).

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Amiloride was added to block airway epithelial sodium absorption. A_2P_4 had little effect when exposed to the basolateral surface of the airway epithelial preparation, but on the luminal surface stimulated additional Cl^- secretion in airway epithelia that had been treated with forskolin. This result is shown in **Figure 1**. Because forskolin maximally activates the CFTR-mediated cAMP-regulated Cl^- channels of airway epithelia, this result suggests that A_2P_4 stimulates luminal purigenic P2U receptors.

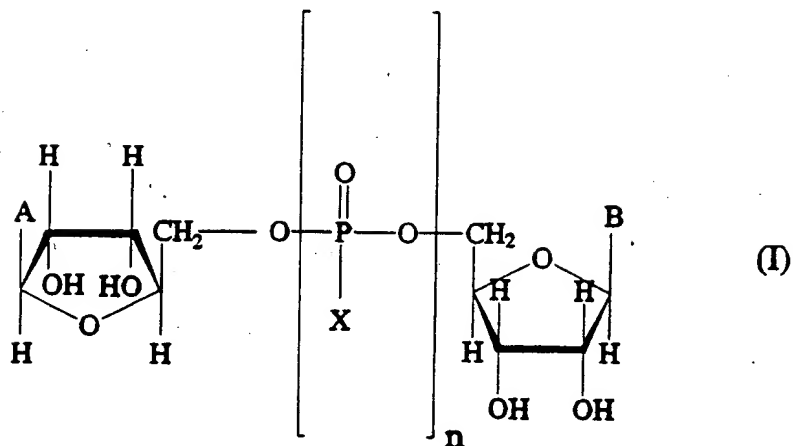
Moreover, the administration of A_2P_4 had no effect on Cl^- secretion in airway epithelia pre-stimulated with UTP, which is known to activate non-CFTR Cl^- channels. These results, shown in **Figure 2**, suggest regulation by A_2P_4 of the non-CFTR Cl^- channel that is controlled by purigenic receptors and further suggests that A_2P_4 stimulates the same airway epithelial Cl^- channels as UTP acting through P2U receptors. Stimulation of this receptor is a therapeutic strategy for certain lung diseases, including cystic fibrosis.

The foregoing Example is illustrative of the present invention, and are not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

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THAT WHICH IS CLAIMED IS:

1. A compound of Formula (I):



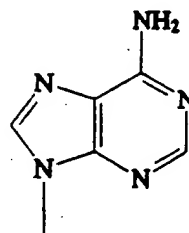
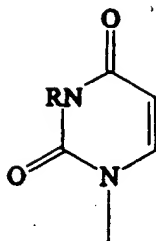
wherein:

n is from 1 to 6;

X is -OH or -SH;

5 and A and B are each independently selected from the group consisting of:

and



wherein R is H or Br;

or a pharmaceutically acceptable salt thereof.

10

2. A compound according to claim 1, wherein n is 4.

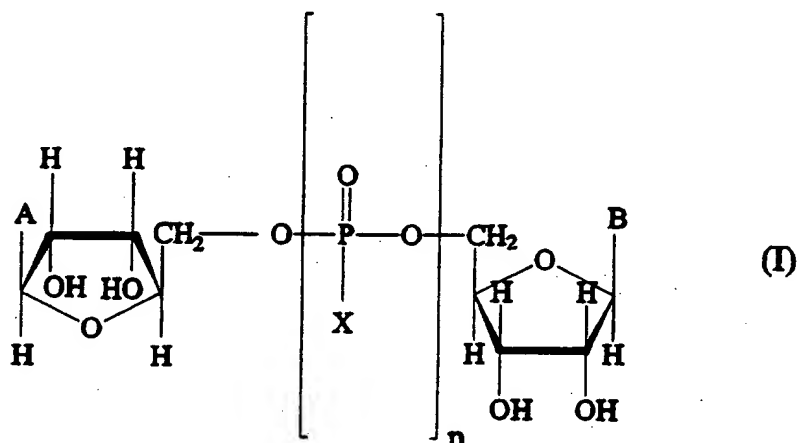
-12-

3. A compound according to claim 1, wherein A and B are selected from the group consisting of uridine and 5-bromouridine.

4. A compound according to claim 1, wherein A and B are adenosine.

5. A compound according to claim 1, wherein X is -OH.

6. A pharmaceutical formulation comprising, in an amount effective to hydrate lung mucous secretions, a compound of Formula (I):



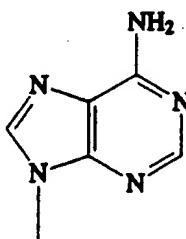
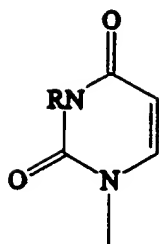
wherein:

n is from 1 to 6;

X is -OH or -SH;

and A and B are each independently selected from the group consisting of:

and



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wherein R is H or Br;

or a pharmaceutically acceptable salt thereof;

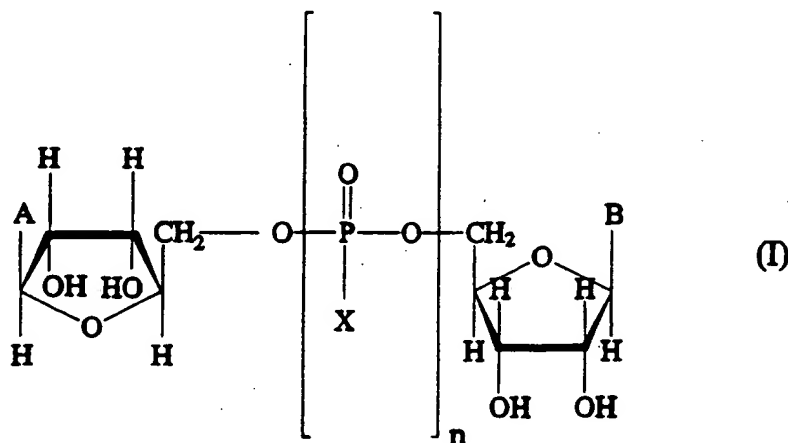
in a pharmaceutically acceptable carrier.

7. A pharmaceutical formulation according to
5 claim 6, further comprising a compound selected from the group consisting of amiloride, benzamil and phenamil to said subject in an amount effective to inhibit the reabsorption of water from lung mucous secretions.

8. A pharmaceutical formulation according to
10 claim 6, wherein said carrier is a liquid carrier.

9. A pharmaceutical formulation according to claim 6, wherein said carrier is a solid particulate carrier.

10. A method of hydrating mucous secretions in
15 the lungs of a subject in need of such treatment, comprising administering to the lungs of the subject a compound of Formula I below, or a pharmaceutically acceptable salt thereof, in an amount effective to hydrate lung mucous secretions:



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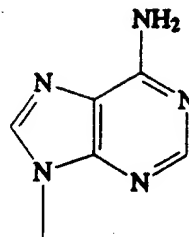
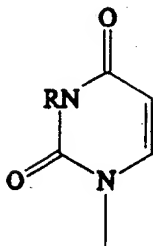
wherein:

n is from 1 to 6;

X is -OH or -SH;

and A and B are each independently selected
5 from the group consisting of:

and



wherein R is H or Br.

11. A method according to claim 10, wherein
said compound is delivered by administering an aerosol
10 suspension of respirable particles comprised of said
compound to the lungs of said subject.

12. A method according to claim 11, wherein
said particles are selected from the group consisting of
solid particles and liquid particles.

13. A method according to claim 11, wherein
15 said aerosol is comprised of particles having a particle
size within the range of about 1 to 10 microns.

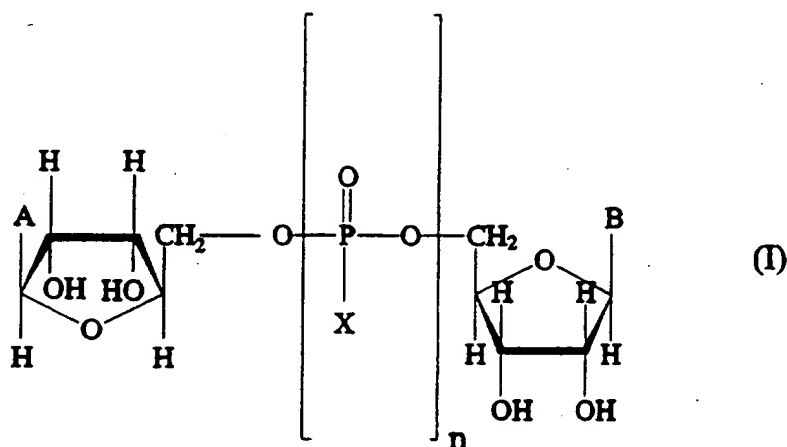
14. A method according to claim 10, wherein
said compound is administered in an amount sufficient to
20 achieve concentrations thereof on the airways surfaces of
said subject of from about 10^{-7} to 10^{-3} Moles/liter.

15. A method according to claim 10, further
comprising concurrently administering a compound selected

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from the group consisting of amiloride, benzamil and phenamil to said subject in an amount effective to inhibit the reabsorption of water from lung mucous secretions.

- 5 16. A method of treating cystic fibrosis in a human subject in need of such treatment, comprising administering by inhalation an aerosol suspension of respirable particles to the respiratory system of said subject, said particles comprised of a compound of
10 Formula I below, or a pharmaceutically acceptable salt thereof:



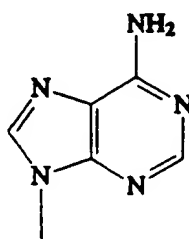
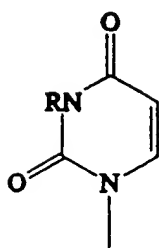
wherein:

n is from 1 to 6;

X is -OH or -SH;

- 15 and A and B are each independently selected from the group consisting of:

and



wherein R is H or Br;
in an amount effective to hydrate retained lung mucous
secretions in the lungs of said subject, whereby the
retained mucous secretions are more easily transported
5 from the lungs via mucociliary action.

17. A method according to claim 16, wherein
said compound is delivered by administering an aerosol
suspension of respirable particles comprised of said
compound to the lungs of said subject.

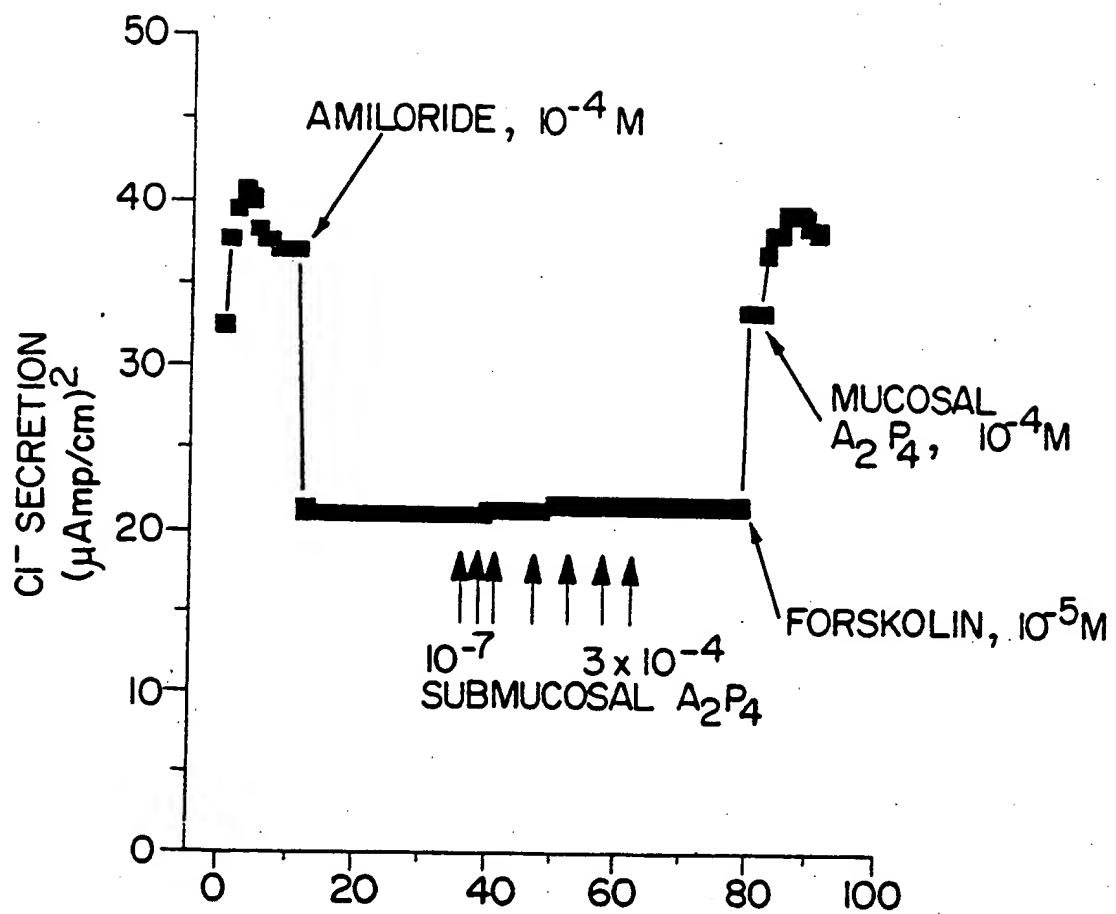
10 18. A method according to claim 17, wherein
said particles are selected from the group consisting of
solid particles and liquid particles.

19. A method according to claim 17, wherein
said aerosol is comprised of particles having a particle
15 size within the range of about 1 to 10 microns.

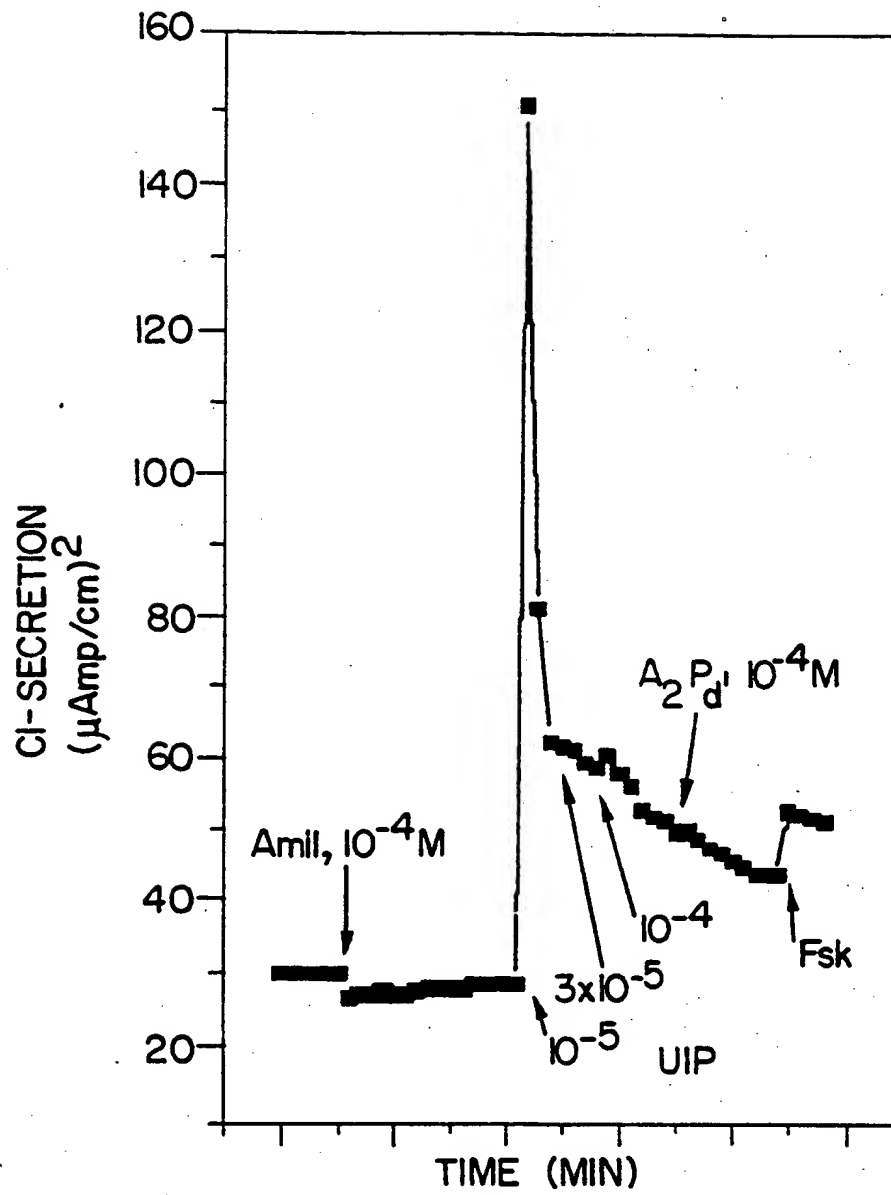
20. A method according to claim 16, wherein
said compound is administered in an amount sufficient to
achieve concentrations thereof on the airways surfaces of
said subject of from about 10^{-7} to 10^{-3} Moles/liter.

20 21. A method according to claim 16, further
comprising concurrently administering a compound selected
from the group consisting of amiloride, benzamil and
phenamil to said subject in an amount effective to
inhibit the reabsorption of water from lung mucous
25 secretions.

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FIG. 1.

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FIG. 2.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/09190

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 9/12

US CL : 424/45

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/45

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,292,498 A (BOUCHER, JR.) 08 March 1994, see entire document.	1-21

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

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Date of the actual completion of the international search

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